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## **Does the Stria Terminalis Carry Information Concerning Feeding and Body Weight Regulation from the Posterodorsal Amygdala to the Hypothalamus?**

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DOES THE STRIA TERMINALIS CARRY INFORMATION CONCERNING FEEDING AND  
BODY WEIGHT REGULATION FROM THE POSTERODORSAL AMYGDALA TO THE  
HYPOTHALAMUS?

A Dissertation

Submitted to the Graduate Faculty of the  
University of New Orleans  
in partial fulfillment of the  
requirements for the degree of

Doctor of Philosophy  
in  
Psychology

by

Bethany Layla Rollins

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M.S. University of New Orleans, 1999

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## Abstract

Previous research has demonstrated body weight gain in rats after lesions to the posterodorsal amygdala. Likewise, a recent study also found increased body weight as a result of knife-cuts of the stria terminalis, just as it exits the amygdala. In the present study, these findings were extended and previous studies replicated by producing 1) lesions in the stria terminalis as it travels dorsally through the brain, 2) coronal knife-cuts anterior to the ventromedial hypothalamus, and 3) axon-sparing lesions of the posterodorsal amygdala using ibotenic acid. Both lesions of the dorsal stria terminalis and coronal knife-cuts anterior to the ventromedial hypothalamus resulted in significant weight gain in female rats as compared to controls. The failure of previous research to find effects after these treatments is attributed to the use of male animals. In addition, examination of anterograde degeneration using an amino-cupric-silver stain in two rats with knife-cuts revealed degenerating terminals in the shell of the VMH and the premammillary nuclei, indicating that the dorsal component of the stria terminalis had been severed. The results of ibotenic acid lesions of the posterodorsal amygdala are unable to be reported due to the inability to histologically verify the lesions. This may have been caused by acid seepage into the lateral ventricles. While the amygdala can not be confirmed as the origin of information concerning body weight regulation and food intake, the stria terminalis does seem to carry this information, exerting an inhibitory influence on the ventromedial hypothalamus.

## Introduction

### Historical Synopsis

Feeding behavior and the regulation of body weight have long been topics of interest for scientists as these complex processes are fundamental to all creatures of the animal kingdom. Traditionally, the hypothalamus has been the structure of interest in the study of body weight regulation and feeding behavior. Investigations into the role of the hypothalamus in feeding began in 1939 with Hetherington and Ranson, who were the first to report obesity in rats given lesions of the ventromedial hypothalamus (VMH). However, a possible role for the temporal lobes in feeding behavior was noted as early as 1888 by Brown and Schafer, who performed partial or complete temporal lobectomies on monkeys, after which the operated monkeys evidenced increased appetite and the tendency to explore everything, including familiar objects and other monkeys, with their mouths.

Subsequent studies investigated the effects of lesions in specific temporal lobe structures, particularly the amygdala, on feeding behavior and body weight regulation in a variety of species, including cats (Green, Clemente, & deGroot, 1957; Morgane & Kosman, 1957; Wood, 1958) and dogs (Fonberg, 1971; Fonberg, 1976; Fuller, Rosvold, & Pribram, 1957). Even though these studies indicated hyperphagia and weight gain following amygdala lesions, interest in the temporal lobes waned with the failure to find consistent effects of lesions in the amygdala on feeding behavior and weight regulation in rats (Anand & Brobeck, 1952; Cole, 1977; Collier & Gault, 1969; Crow & Whitaker, 1970; Czech, 1973; Dacey & Grossman, 1977; Fitzgerald & Burton, 1981; Grossman & Grossman, 1963; Kemble & Godding, 1981; Kemble, Studelska, & Schmidt, 1979; Koikegami, Fuse, Hiroki, Kazami, & Kageyama, 1958; Lorenzini, Baldi, Bucherelii, Giachetti, & Tassoni, 1991; Pubols, 1966; Rosen, 1968; Schoenfeld & Hamilton,

1981; Schwartz & Kling, 1964; Sclafani, Belluzzi, & Grossman, 1970; Stoller, 1972; Stoller & Stoller, 1978). Thus, researchers focused almost exclusively on the hypothalamus as a regulator of body weight and ingestive behavior.

Interest in the role of the amygdala in ingestion and body weight control has been revived with the discovery of significant and lasting weight gain in rats with lesions to the most posterodorsal aspects of the amygdala (King, Kass, Cadieux, et al., 1993; King, Kass, Neville, et al., 1993). The most effective lesions for producing weight gain include the posterodorsal division of the medial amygdaloid nucleus as well as the intra-amygdaloid bed nucleus of the stria terminalis (BSTIA) (Rollins & King, 2000). This area will be referred to as the posterodorsal amygdaloid area (PDA). The major anatomical pathway between these areas of the amygdala and the hypothalamus is the stria terminalis (Canteras, Simerly, & Swanson, 1995; de Olmos, 1972; Heimer, 1995; Isaacson, 1982). These findings have stimulated additional research into the respective roles of the amygdala, stria terminalis, and medial hypothalamus and their interactions in the control of ingestive behavior and weight regulation. Before discussing the nature of the connections among these structures, a more detailed account of the findings of researchers investigating the effects of VMH and temporal lobe/amygdala lesions is in order.

### The Hypothalamus

Although Hetherington and Ranson were the first to systematically investigate the effects of VMH lesions on rats in 1939, obesity in humans with tumors in the VMH was noted as early as 1840, and this was known as Frohlich's syndrome (Bray & Gallagher, 1975). Later, investigators found that VMH lesions in other species such as cats and primates also resulted in hyperphagia and obesity (Anand, Dua, & Shoenberg, 1955). Many studies have been performed to determine the characteristics and etiology of the VMH syndrome. Two stages of ingestive

behavior are observed (Brooks & Lambert, 1946). The dynamic stage, lasting for approximately 1 month after surgery, is characterized by hyperphagia and rapid weight gain (Brooks & Lambert, 1946). In fact, animals will often begin eating voraciously before they completely awaken from surgery and double their body weights within 30-40 days postoperatively (Brobeck, Tepperman, & Long, 1943). In the static stage that follows, food intake returns to normal but the increased weight is maintained (Brooks & Lambert, 1946).

Not only do rats with VMH lesions eat more, they also evidence disruption of normal feeding patterns, eating larger, more frequent meals during the day rather than at night as do normal rats (Becker & Kissileff, 1974; Teitelbaum & Campbell, 1958). In addition, evidence exists implicating a metabolic deficit in VMH weight gain as VMH rats pair-fed with normal rats also gain excess weight (Han, 1967). VMH rats have also been found to be hypersinsulinemic even in the absence of increased food consumption (Hales & Kennedy, 1964). Because lesions of the VMH produce overeating, this area came to be referred to as the satiety center (Anand & Brobeck, 1951).

Later, other areas in the hypothalamus, particularly the lateral hypothalamus (LH) and the paraventricular nucleus (PVN), were also found to affect ingestive behavior and weight gain when lesioned. Destruction of the lateral hypothalamus results in aphagia, adipsia, and hypoinsulinemia (Anand & Brobeck, 1951). Accordingly, the lateral hypothalamus became known as the feeding center. Similar to VMH lesions, lesions of the paraventricular nucleus (PVN) also result in overeating and obesity, though not to the degree of that observed with VMH lesions (Aravich & Sclafani, 1983; King & Gaston, 1977; Tokunaga, Fukushima, Kemnitz, & Bray, 1986; Tokunaga et al., 1989; Tokunaga et al., 1991). Also, insulin levels are elevated only under ad libitum conditions after PVN lesions, while VMH lesions result in higher insulin levels

under both ad libitum and food-restricted conditions (King, Zansler, Michel, Kelly, & Frohman, 1989; Leibowitz, Hammer, & Chang, 1981).

Imaging studies in human subjects confirm a role for the hypothalamus in feeding and weight regulation. PET studies have found a correlation between hypothalamic activation and hunger ratings, with greater activity in the hypothalamus as subjects indicated increased hunger (Morris & Dolan, 2001; Tataranni et al., 1999). Accordingly, regional cerebral blood flow to the hypothalamus decreased once the fasting subjects were fed (Morris & Dolan, 2001). Using fMRI with temporal clustering analysis, decreased activity after ingestion of glucose solution was seen in the medial hypothalamus (Liu, Gao, Liu, & Fox, 2000) and specifically in the VMH (Liu & Gold, 2003). This decreased hypothalamic activity was found to correlate with plasma insulin levels (Liu et al., 2000; Liu & Gold, 2003). Furthermore, the reduction in VMH activity in response to administration of glucose solution has been found to be less in magnitude and delayed in obese subjects (Matsuda et al., 1999). A decrease in PVN activity in response to glucose was also noted in this study, but this phenomenon was non-specific as activity in the PVN also decreased in response to ingestion of water in the control condition (Matsuda et al., 1999). Gautier et al. (2000) also noted a smaller decrease in hypothalamic activity as measured by fMRI in response to a liquid meal in obese men as compared to lean men. In another fMRI study, hypothalamic activity was increased in subjects when they were shown pictures of high-calorie foods, but not when they were shown pictures of low-calorie foods or eating utensils (Killgore et al., 2003). Also, a negative correlation between serum leptin levels and hypothalamic activation as measured by PET was found in fasting obese but not lean women who were exposed to food (Karhunen, Lappalainen, Vanninen, Kuikka, & Uusitupa, 1999).

## The Temporal Lobes and the Amygdala

As mentioned previously, several early studies of temporal lobe function implicated the amygdala in ingestive behavior and weight regulation after lesions in cats (Green et al., 1957), dogs (Fuller et al., 1957), monkeys (Brown & Schafer, 1888; Bucy & Kluver, 1955), and humans (Terzian & Ore, 1955) resulted in hyperphagia. Temporal lobectomies in rhesus monkeys have resulted in hyperphagia, consumption of species-atypical foods, and obesity (Brown & Schafer, 1888; Bucy & Kluver, 1955; Pribram & Bagshaw, 1953). Similarly, Terzian and Ore (1955) reported a case in which a human ate four times as much as normal after undergoing a temporal lobectomy to alleviate epilepsy.

Neuroimaging studies reveal that the amygdala is often activated in response to stimuli that signal food. For instance, increased regional cerebral blood flow to the amygdala (as measured by PET) was noted when satiated subjects read high-incentive menus, and this increased response was correlated with individual subject ratings of menu items (Arana et al., 2003). Another PET study found a correlation between regional cerebral blood flow in the left amygdala and recognition memory of food items, and both of these measures declined as hungry subjects became satiated (Morris & Dolan, 2001). No amygdala activity was seen in response to non-food items (Morris & Dolan, 2001). Similarly, hungry subjects presented with pictures of food evidenced amygdala activation as measured by fMRI (LaBar et al., 2001). No amygdala activity was noted once subjects were satiated or when the subjects were presented with pictures of tools (LaBar et al., 2001). Another fMRI study found an increase in amygdala activity in subjects when they were presented with pictures of both high-calorie and low-calorie foods, but not when pictures of eating utensils were shown (Killgore et al., 2003). Also, an additional fMRI study found increased activity specifically in the posterior dorsal amygdala in response to stimuli

that signaled the impending delivery of a pleasant taste (glucose), but not to stimuli that signaled an aversive or neutral taste (O'Doherty, Deichmann, Critchley, & Dolan, 2002). Other studies have found that aversive odors (Zald & Pardo, 1997) and tastes (Zald, Lee, Fluegel, & Pardo, 1998) resulted in increased regional cerebral blood flow in the amygdala, though amygdala activation to both pleasant and unpleasant tastes has been noted by some (O'Doherty, Rolls, Bowtell, & McGlone, 2001). Moreover, neuronal activity in the region of the amygdala was found to decrease in obese but not lean women in response to satiation (Gautier et al., 2001)

#### The posterodorsal amygdala.

Despite the various lines of research implicating the amygdala in ingestive behavior, this structure has largely been ignored after attempts to produce lesions that reliably affect feeding behavior and body weight regulation in rats failed (see King, Kass, Cadieux, et al., 1993 and Rollins & King, 2000 for a review). However, in recent years interest in the role of the amygdala in ingestive behavior has been revived with the discovery of King, Kass, Cadieux, et al., (1993) and King, Kass, Neville, et al., (1993) of robust increases in body weight and food intake in rats with lesions placed in the posterodorsal amygdala (PDA). Rats with bilateral lesions of the posterodorsal amygdala double their food intake and gain 20-30 grams within a few days after surgery (King et al., 1998; King, Kass, Neville, et al., 1993). Typically, body weight increases by 50-80 grams within 20 days postoperatively while normal rats gain 5-15 grams in the same period (King et al., 1998; King, Kass, Neville, et al., 1993). These weight gains are less than those observed with lesions to the VMH, but comparable to gains observed with lesions to the PVN (Aravich & Sclafani, 1983; Tokunaga et al., 1986). Lesions of structures surrounding the PDA, including the basolateral and corticomedial amygdaloid nuclei, do not result in weight gain unless they impinge upon the PDA (Rollins & King, 2000). Furthermore, the overlying globus

pallidus is often damaged with PDA lesions, and this has been found to attenuate weight gains (King, Cook, et al., 2003; Rollins & King, 2000).

Animals with posterodorsal amygdala lesions are similar in some respects to animals with VMH lesions. Both lesions result in hypersinsulinemia during restricted and ad lib feeding conditions (Hales & Kennedy, 1964; King, Cook, & Dallman, 1996; King & Frohman, 1982), both produce greater weight gains in female animals (Cox, Kakolewski, & Valenstein, 1969; King et al., 1999; King & Frohman, 1982; Singh, 1970; Valenstein, Cox, & Kakolewski, 1969), and unilateral lesions in both areas produce weight gains (King, Cook, et al., 2003; Mayer & Barnett, 1955). Animals with posterodorsal amygdala lesions progress through dynamic and static phases similar to VMH animals (Brooks & Lambert, 1946; King, Kass, Neville, et al., 1993). Also, neither VMH- lesion animals (Strominger, Brobeck, & Cort, 1953; Teitelbaum, 1955) nor posterodorsal-lesion animals (King et al., 1998) adjust their caloric intake when their food is adulterated with non-nutritive bulk. However, unlike VMH-lesion animals, rats with posterodorsal amygdala lesions prefer carbohydrates whereas VMH-lesion animals prefer fats (Carlisle & Stellar, 1969; Corbit & Stellar, 1964; King et al., 1998). Moreover, posterodorsal amygdala lesions do not appear to produce a hyper-responsivity to switch in diets as do VMH lesions (King et al., 1998; King, Kass, Cadieux, et al., 1993; King, Rossiter, Cook, & Sam, 1997; Teitelbaum, 1955).

### Anatomical Considerations

As is evident, several similarities exist between animals with posterodorsal amygdala lesions and ventromedial hypothalamic lesions. Accordingly, analysis of axonal degeneration by the cupric silver method indicates substantial degeneration in the VMH following PDA lesions (King, Cook, et al., 2003). No degeneration has been found in the PVN following these lesions



(King, Cook, et al., 2003). Obviously, important connections exist between the amygdala and VMH, possibly allowing them to work together in the control of aspects of feeding behavior and weight regulation.

Situated in the medial temporal lobe anterior to the hippocampus, the amygdala as a whole receives afferent fibers from the olfactory bulb, the olfactory tubercle, the pyriform cortex, and from diencephalic structures such as the hypothalamus (Cowan, Raisman, & Powell, 1965). The amygdala itself may be subdivided into three areas (Heimer, 1995). The basolateral amygdala receives input from sensory association areas, connects reciprocally with the cortex, and influences sensory processing (Heimer, 1995). The olfactory/cortical amygdala receives input from olfactory areas and sends efferents to the hypothalamus and centromedial amygdala (Heimer, 1995). The centromedial and extended amygdala (Alheid & Heimer, 1988) includes the centromedial amygdala and the bed nucleus of the stria terminalis (BNST), which are directly continuous with each other through the area of the substantia innominata (Heimer, 1995). This area receives afferents from the hippocampus, insula, orbitofrontal cortex, and basolateral amygdala and sends efferents to the hypothalamus and brain stem via the stria terminalis and ventral amygdalofugal pathway (Heimer, 1995).

The extended amygdala may be divided into central and medial components (Alheid, de Olmos, & Beltramino, 1995). The medial amygdala specifically receives accessory olfactory inputs (from the vomeronasal organ) and main olfactory inputs (Canteras et al., 1995). In addition, it has many connections with other parts of the amygdala as well as substantial intrinsic connections (Canteras et al., 1995). Significant reciprocal connections via the stria terminalis exist between the medial subdivision and the posterodorsal amygdala and medial hypothalamus. (Alheid et al., 1995; Canteras et al., 1992, 1994, 1995; Heimer, 1995). The medial amygdala also

sends fibers to olfactory pathways, the hippocampus, the ventral striatum, the ventral pallidum, the BNST, the thalamus, the periaqueductal gray (PAG), the ventral tegmental area (VTA), and the midbrain raphe (Canteras et al., 1995).

The medial amygdala can be further partitioned (according to cytoarchitectural differences) into ventral and dorsal divisions (Canteras et al., 1995). The ventral division consists of anterodorsal, anteroventral, and posteroventral components while the dorsal division consists of a posterodorsal component (Canteras et al., 1995). As the posterodorsal subdivision is of primary interest, and it demonstrates unique connections in relation to the ventral components (Canteras et al., 1995), it will be addressed in more detail than the other subdivisions.

Further support for these divisions and the singularity of the posterodorsal component is demonstrated by their differential connections as examined using *Phaesolus vulgaris* leucoagglutinin (PHAL) in male rats (Canteras et al., 1995). The ventral subdivisions are substantially interconnected but the posterodorsal subdivision does not demonstrate many connections with other aspects of the medial amygdala (Canteras et al., 1995). The posterodorsal subdivision projects strongly to the principle nucleus of BNST while the other subdivisions project to the transverse and interfascicular nuclei of the BNST (Canteras et al., 1995). The principle nucleus of the BNST in turn projects back to the posterodorsal division as well to hypothalamic areas innervated by the posterodorsal division (Canteras et al., 1992). In addition, the ventral subdivision provides a much more substantial projection to the thalamus than does the dorsal division (Canteras et al., 1995).

When examined closely, the ventral and dorsal divisions of the medial amygdala also show differential projections to hypothalamic structures. The components of the ventral division project to the lateral aspects of the medial preoptic area, while the posterodorsal subdivision

densely innervates the central and medial aspects of the medial preoptic area, as well as the anteroventral periventricular nucleus, a region neglected by other parts of the medial amygdala (Canteras et al., 1995). The caudal preoptic area receives projections from all four subdivisions of the medial amygdala (Canteras et al., 1995). The ventral premammillary nucleus also receives projections from all subdivisions, but the posterodorsal subdivision provides the most fibers and is itself significantly innervated by the ventral premammillary nucleus (Canteras et al., 1994, 1995).

#### PDA lesions.

Similar projection patterns have been noted for the posterodorsal amygdala using the silver degeneration method in female rats following electrolytic lesions of the PDA (King, Cook, et al., 2003). Anterograde degeneration after PDA lesions was noted in the lateral septum, the shell of the nucleus accumbens, the medial division of extended amygdala, the medial preoptic nucleus, the retrochiasmatic area, the VMH, and the premammillary nucleus. However, it is suspected that the degeneration seen in the nucleus accumbens was not directly due to damage to the PDA (King, Cook, et al., 2003).

The PDA lesions that produce the greatest weight gains include the posterodorsal portion of the medial amygdala and the intra-amygdaloid bed nucleus of the stria terminalis (BSTIA) (Rollins & King, 2000). Regression analysis has shown that damage to the medial amygdala, BSTIA, and the globus pallidus accounts for 97% of the variance in observed weight gains (Alheid et al., 2000). The BSTIA is found dorsally between the medial and central nuclei (Alheid et al., 1995). The cells of this structure are interspersed with fibers that are gathering to form the columns of the stria terminalis. Accordingly, similar connections exist between the BSTIA and the relevant portion of the medial amygdala (King, Cook, et al., 2003). Both areas connect

reciprocally with the other components of the medial extended amygdala as well as the medial hypothalamus. In fact, one of the five main pathways out of the VMH innervates the BNST and the central and medial nuclei of the amygdala (Krieger et al., 1979; Saper et al., 1976).

#### Stria terminalis.

The posterodorsal subdivision of the medial amygdala travels medially along the tip of the temporal horn of the lateral ventricle with the stria terminalis (Canteras et al., 1995). Given this close association, it is not surprising that the stria terminalis is the major pathway out of the posterodorsal subdivision (Canteras et al., 1995). Moreover, the PDA contains fibers of passage from both the stria terminalis and ventral amygdalofugal pathway, fiber systems that connect the amygdala with the basal forebrain and hypothalamus (Alheid et al., 1995; Canteras et al., 1994, 1995; de Olmos, 1972; Petrovich, Risold, & Swanson, 1996).

In fact, the amygdala as a whole is closely associated with the stria terminalis. The stria terminalis is the main conduit of fibers from the cortical, medial, and central nuclei of the amygdala while the basolateral fibers are carried in both the stria terminalis and the ventral amygdalofugal pathway (Cowan et al., 1965). The main targets of the stria terminalis fibers are the septum and the hypothalamus (Canteras et al., 1995; Klingler & Gloor, 1960). Stria fibers travelling to the hypothalamus originate mainly in the cortical nuclei and the periamygdaloid cortex and end in the lateral preoptic nucleus, the medial preoptic area, the anterior nuclei, and the ventromedial nuclei (Ishikawa, Kawamura, & Tanaka, 1969). The preoptic area also receives fibers from the medial amygdala, which is a main provider of stria inputs to the BNST as well (Alheid et al., 1995; de Olmos, 1972; Ishikawa et al., 1969; Kevetter & Winans, 1981; Krettek & Price, 1978). More specifically, the posterodorsal division of the medial amygdala sends fibers to the septal area, the infralimbic area of the prefrontal cortex, and hypothalamic nuclei via the stria

terminalis (Canteras et al., 1995). Furthermore, not only does the stria carry fibers from the amygdala to other structures, it also innervates the amygdala, providing input from other structures, such as the preoptic area and the rostral hypothalamus (Cowan et al., 1965).

The stria terminalis begins to take shape in the intra-amygdaloid division of the bed nucleus of the stria terminalis as fibers from different areas of the amygdala converge. From here the stria terminalis runs adjacent to the roof of the inferior horn of the lateral ventricle (Klingler & Gloor, 1960). As the stria travels along this path toward the lateral geniculate nucleus, it passes medial to the tail of the caudate nucleus and lateral to the optic tract (Klingler & Gloor, 1960). Once the roof of the inferior horn of the ventricle curves up and becomes the floor of the lateral ventricle, the stria travels through the floor and between the thalamus and the caudate nucleus (Klingler & Gloor, 1960). As it continues anteriorly, the stria runs along the dorsomedial surface of the internal capsule, and once it passes the foramen of Monro and reaches the anterior commissure, the stria splits into subcomponent tracts (Cowan et al., 1965; Klingler & Gloor, 1960).

Various studies utilizing a number of species have traced the subcomponents of the stria terminalis. The first subcomponent to be discussed (see Table 1) will be referred to as the dorsal component, but it has also been known as the supracommissural, the precommissural, or the subventricular component (Ban & Omukai, 1959; de Olmos, 1972; Heimer & Nauta, 1969; Ishikawa et al., 1969; Klingler & Gloor, 1960). This component runs in a caudal direction over the rostral anterior commissure (Heimer & Nauta, 1969). Klingler and Gloor (1960) described this dorsal component as terminating in the BNST, the nucleus accumbens septi, and the anterior perforated space of the human brain. Ishikawa et al. (1969) found this component to originate in the periamygdaloid cortex and the medial and cortical nuclei of the amygdala and to terminate in

the medial preoptic area, the anterior hypothalamic nucleus, and the VMH of the cat. Using rabbits, Ban and Omukai (1959) described this component as originating in the medial, cortical, and basal nuclei of the amygdala and terminating in the BNST, the septum, and the VMH. Heimer and Nauta (1969) found the dorsal component in the rat to terminate in the shell of the VMH and in the ventral premammillary nucleus. Also using rats, de Olmos (1972) described this component as originating in the cortical and medial amygdaloid nuclei and terminating in the BNST, the lateral septal nucleus, the nucleus accumbens septi, the medial preoptic area, the shell of the VMH, the premammillary area, and olfactory areas such as the olfactory tubercle, the anterior olfactory nucleus, and the granular layer of the accessory bulb. Thus, in rats there seems to be some consensus that the stria terminalis sends fibers to the shell of the VMH and the premammillary area (de Olmos, 1972; Heimer & Nauta, 1969). In addition, there is also a lot of support for termination points in the BNST, the septum, the medial preoptic area, and the nucleus accumbens septi in a variety of species (Ban & Omukai, 1959; de Olmos, 1972; Heimer & Nauta, 1969; Ishikawa et al., 1969; Klingler & Gloor, 1960).

Table 1. Summary of Studies Detailing the Origination and Termination of the Dorsal Component of the Stria Terminalis

	Ban & Omukai, 1959	de Olmos, 1972	Heimer & Nauta, 1969	Ishikawa et al., 1969	Klingler & Gloor, 1960
Species	Rabbit	Rat	Rat	Cat	Human
Origins	Medial, cortical, and basal nuclei of amygdala	Medial and cortical nuclei of amygdala		Medial and cortical nuclei of amygdala, periamygdaloid cortex	
Terminations	BNST, septum, VMH	BNST, lateral septal nucleus, medial preoptic area, nucleus accumbens septi, premammillary area, shell of the VMH, olfactory areas	Shell of VMH, ventral premammillary nucleus	Anterior hypothalamic nucleus, medial preoptic area, VMH	Anterior perforated space, BNST, nucleus accumbens septi

The ventral component (see Table 2), also known as the postcommissural, the preoptic, the hypothalamic, or the juxtacapsular component, is another commonly described subcomponent of the stria terminalis (Ban & Omukai, 1959; de Olmos, 1972; Heimer & Nauta, 1969; Ishikawa et al., 1969; Klingler & Gloor, 1960). This component has been found to originate in the basal nucleus of the amygdala and the periamygdaloid cortex (Ban & Omukai, 1959) and to terminate in the preoptic area (Klingler & Gloor, 1960), particularly the lateral preoptic area (Ban & Omukai, 1959; Ishikawa et al., 1969), the junction of the medial preoptic area and hypothalamus (de Olmos, 1972), the BNST (de Olmos, 1972; Heimer & Nauta, 1969; Ishikawa et al., 1969; Klingler & Gloor, 1960), the anterior hypothalamus (Heimer & Nauta,

1969; Klingler & Gloor, 1960), the thalamus (Klingler & Gloor, 1960), the VMH (de Olmos, 1972), and the premammillary area (de Olmos, 1972).

Table 2. Summary of Studies Detailing the Origination and Termination of the Ventral Component of the Stria Terminalis

	Ban & Omukai, 1959	de Olmos, 1972	Heimer & Nauta, 1969	Ishikawa et al., 1969	Klingler & Gloor, 1960
Species	Rabbit	Rat	Rat	Cat	Human
Origins	Basal nucleus of amygdala, periamygdaloid cortex				
Terminations	Lateral preoptic area	BNST, junction of medial preoptic area and hypothalamus, premammillary area, VMH	Anterior hypothalamic nucleus, BNST	BNST, lateral preoptic area	Anterior hypothalamus, BNST, preoptic area, thalamus

The final subcomponent of the stria terminalis is the commissural component. This component connects the ipsilateral and contralateral amygdali via the anterior commissure (de Olmos, 1972; Ishikawa et al., 1969).

The stria terminalis provides the means for the amygdala to regulate activity in the preoptic area and the medial hypothalamus, areas themselves involved in motivated behaviors such as feeding (Isaacson, 1982). Accordingly, after PDA lesions that produce weight gain, heavy anterograde degeneration was observed in the stria terminalis and the VMH, along with more minor degeneration in other targets of the stria such as the septum, the nucleus accumbens, and the medial hypothalamus (King, Cook, et al., 2003). Recently, weight gains have been



produced in rats after transections of the stria terminalis at the point where it exits the amygdala (King, Rollins, et al., 2003). In this study, female rats with bilateral knife-cuts of the stria terminalis gained an average of 35.9 grams over 20 days as compared to a gain of 0.1 grams for the operated controls (King, Rollins, et al., 2003). Previous studies investigating the effects of stria terminalis destruction interrupted the stria farther along its course as it ascends from the amygdala (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975). No significant effects on body weight or food intake were observed in these studies (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975). However, these studies used male rats, and as noted previously, the effects of PDA and VMH lesions are much more pronounced in female rats (Cox et al., 1969; King et al., 1999; King & Frohman, 1982; Singh, 1970; Valenstein et al., 1969).

Given the results obtained in female rats with knife-cuts of the stria terminalis close to its point of origin, it is of some interest to investigate the effects of interrupting the stria terminalis farther along its course before it reaches its various targets, thereby duplicating previous studies (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975). However, unlike in these previous studies, female rats will be used in the present investigation for reasons noted above. Also, given the relationship between the PDA and the VMH and the effects of electrolytic lesions at these sites, it will also be of interest to sever the stria terminalis just as it enters the VMH. Earlier studies employing coronal knife-cuts anterior to the VMH yielded mixed results, with some finding weight gains and/or hyperphagia in female rats (Grossman, 1971; Palka, Coyer, & Critchlow, 1969; Storlien & Albert, 1972) and some male rats (Paxinos & Bindra, 1972) and others finding no effects on weight or feeding in female (Sclafani, 1971) or male rats (Voloschin, Joseph, & Knigge, 1968). While it is very possible that the stria terminalis was

severed as it curves around to enter the VMH anteriorly in these studies, none of the above researchers confirmed that their cuts indeed severed fibers entering the VMH. Thus, axonal degeneration analysis using the amino-cupric-silver tracing method will be utilized in the present study to identify the termination points of the cut fibers (de Olmos, Beltramino, & de Olmos de Lorenzo, 1994).

As previous studies (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975) found no effects of interrupting the stria terminalis near its midpoint on feeding and body weight regulation, the possible role of the stria terminalis in communicating between the amygdala and the VMH was disregarded in this respect. However, by interrupting the stria terminalis at its midpoint and termination point, in combination with the previous study (King, Rollins, et al., 2003) cutting the stria terminalis at its origins (see Fig. 1), it is hoped that the question regarding the role of the stria terminalis in communicating information concerning these functions will be answered definitively. It is the major pathway connecting the newly discovered PDA, the locus within the amygdala that produces increases in body weight and food intake when lesioned, and the VMH (Canteras et al., 1995; de Olmos, 1972; Heimer, 1995; Isaacson, 1982; King, Kass, Cadieux, et al., 1993; King, Kass, Neville, et al., 1993). Thus, the stria terminalis is in a prime position to be carrying information from the PDA to the VMH.

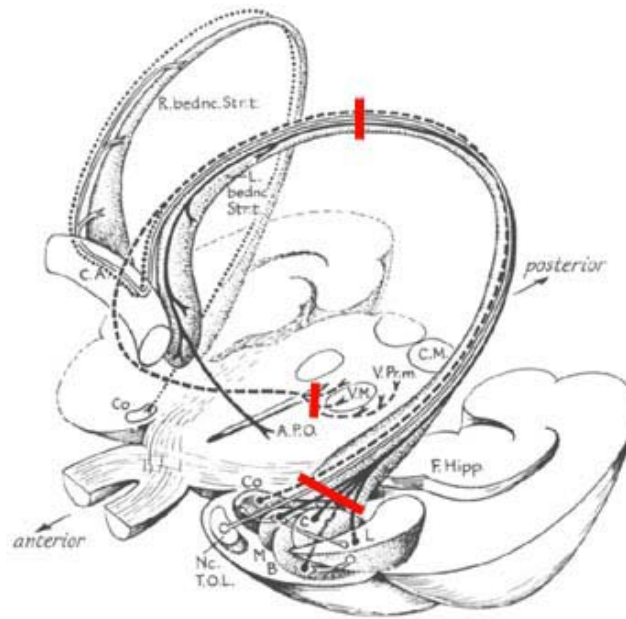


Figure 1. Schematic drawing of the stria terminalis (Lammers, 1972, Fig. 2, p. 131), with lesion and knife-cut sites indicated in red.

Interrupting the stria terminalis at various points may indicate whether feeding relevant information is travelling to the VMH, but it does not confirm the origin of these fibers. Thus, destruction of the PDA using ibotenic acid, an excitotoxin that destroys cell bodies while leaving fibers of passage intact, may provide valuable information as to whether the effects of PDA lesions are the result of damage to cells of the amygdala or to fibers passing through (Jarrard, 1991). This will be an important distinction, as it will permit the assessment of the role of cells within the amygdala itself in body weight regulation. If destruction of the cells of the amygdala is found to produce weight gains, a duplication of VMH function may be indicated, and the possibility that the stria terminalis carries information concerning feeding and body weight from the amygdala to the VMH will be strengthened. Plus, the existence of a feeding-related and/or body weight-regulating circuit running from the PDA to the VMH through the stria terminalis

may be supported or refuted. Thus, it is hoped to further elucidate the anatomical substrates involved in the weight gain resulting from PDA lesions.

## Method

### Subjects

A total of 68 adult female Long-Evans hooded rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing between 240-340 g were utilized. Each animal was individually caged in a temperature-controlled colony (21-24° C) with a 12-hour light-dark cycle (lights on at 3 a.m., lights off at 3 p.m.) throughout the experiment.

### Surgeries

For all surgeries, 85 mg/kg Ketamine HCl plus 10 mg/kg Xylazine were used to anesthetize the animals via intraperitoneal injection. A Kopf small animal stereotaxic instrument (Tujunga, CA) was used to position electrodes and cannulas relative to bregma. Bilateral electrolytic lesions of the dorsal stria terminalis were produced by passing a 1.5 mA anodal current between the uninsulated tip of an insulated stainless steel electrode (Plastics One, Roanoke, VA) and a rectal cathode for 20 sec with 0.4 mm of the electrode tip uninsulated. A pilot study was conducted to determine the optimal coordinates. The coordinates used to produce lesions of the dorsal stria terminalis were 1.8 mm posterior to bregma, 3.6 mm lateral to the midsagittal suture, and 5.6 mm below the surface of the skull, with the upper incisor bar positioned horizontally with the interaural line. Sham lesions were accomplished by drilling holes at the same coordinates and lowering the electrode to the same depth without passing any current.

Bilateral coronal knife cuts anterior to the VMH were produced by a blade cannula containing a retractable wire knife (Kopf model 120). A pilot study was conducted to determine the optimal coordinates. The coordinates used were 0.2 mm posterior to bregma, 1.5 mm lateral to the midsagittal suture, and 10.1 mm below the surface of the skull, with the upper incisor bar

positioned horizontally with the interaural line. The wire knife was extended 1.5 mm medially (with the wire blade curving downward by approximately 0.8 mm) and raised 1.5 mm to cut fibers entering the VMH. The wire blade was then retracted and withdrawn from the skull. Sham knife cuts were accomplished using the same coordinates, with the blade cannula lowered to the same depth without extending the blade.

Bilateral microinjections of ibotenic acid dissolved in phosphate buffer (Sigma Chemical, St. Louis, MO, 10 $\mu$ g/ $\mu$ l) into the posterodorsal amygdala were achieved using a 2.0  $\mu$ l Hamilton syringe. Each side was injected with 0.1  $\mu$ l over the course of 1 min. Following injection, the syringe remained in place for 5 min and was then raised over the course of 1 min. The coordinates used were 1.6 mm posterior to bregma, 4.5 mm lateral to the midsagittal suture, and 8.6 mm below the surface of the skull, with the upper incisor bar positioned horizontally with the interaural line.

## Procedure

### Dorsal stria terminalis.

Two groups of animals were included: female rats with lesions of the dorsal stria terminalis (n = 12) and female rats with sham lesions (n = 8). All animals were fed Harlan Teklad mouse/rat diet LM-485 before and during the experiment. Body weight and food intake (corrected for spillage) were measured daily for 21 days, beginning the day of surgery.

### Anterior ventromedial hypothalamus

Two groups of animals were included: female rats with coronal knife cuts anterior to the VMH (n = 17) and female rats with sham knife cuts (n = 8). All animals were fed Harlan Teklad mouse/rat diet LM-485 before and during the experiment. Body weight and food intake (corrected for spillage) were measured daily for 21 days, beginning the day of surgery. An

additional group of female rats ( $n = 3$ ) were given either coronal knife cuts anterior to the VMH ( $n = 2$ ) or a sham cut ( $n = 1$ ) and sacrificed 48 hrs later for special histological procedures (see below).

#### Ibotenic acid.

Two groups of animals were included: female rats with ibotenic acid microinjected into the posterodorsal amygdala ( $n = 12$ ) and a sham group consisting of female rats microinjected with the phosphate buffer vehicle ( $n = 8$ ). All animals were fed Harlan Teklad mouse/rat diet LM-485 before and during the experiment. Body weight and food intake (corrected for spillage) were measured daily for 21 days, beginning the day of surgery.

#### Histology

Once the experiments were completed, animals with cuts or lesions were sacrificed with a lethal dose of ketamine/xylazine. All animals (excepting the three rats in the anterior hypothalamic group retained for special histological processing) were perfused with physiological saline solution and 10% Formalin solution. Brains were removed and stored in a 10% Formalin solution and subsequently frozen and sliced into 40- $\mu$ m coronal (electrolytic and ibotenic acid lesions) or sagittal (coronal knife cuts) sections. Cresyl violet was used to stain the sections of the brain containing the lesion prior to histological examination under a light microscope. Correct placement of the lesions was determined using the stereotaxic atlas by Paxinos and Watson (1998).

Three animals (two with hypothalamic knife cuts and one with a sham cut) were sacrificed and perfused 48 hours postoperatively using superior reagent grade wash and fix as recommended for the amino-cupric-silver method (de Olmos et al., 1994; King, Cook, et al., 2003). The brains were then shipped to a commercial laboratory specializing in multibrain

technology for cupric-silver degeneration staining (Neuroscience Associates, Knoxville, TN).

This procedure is detailed by Switzer (2000) and summarized by King, Cook et al., (2003).

Amino-cupric-silver staining was employed so that fiber degeneration could be visualized upon histological examination.

### Statistical Analyses

Independent-groups  $t$  tests were performed for each study to assess weight gain and food intake. Inferential tests were conducted with the probability of Type I error set at .05. Statistical results include  $t$ ,  $p$ , and estimated effect size  $g$ .



## Results

### Dorsal Stria Terminalis

Of the 12 rats receiving lesions aimed at the dorsal stria terminalis, 7 sustained bilateral damage to this structure as revealed by histological analysis. In these 7 rats, the internal capsule and the reticular thalamic nuclei were also damaged. Other areas upon which successful lesions often infringed included the striatum ( $n = 4$ ), the laterodorsal thalamic nuclei ( $n = 5$ ), the ventral lateral thalamic nuclei ( $n = 6$ ), the ventral anterior thalamic nuclei ( $n = 2$ ), and the fimbria, either bilaterally ( $n = 3$ ) or unilaterally ( $n = 2$ ). Four rats sustained lesions that missed the intended target, instead damaging the striatum, the reticular thalamic nucleus, and the internal capsule, and the slides for one rat were damaged such that confirmation of the lesion could not be made. Successful lesions can be seen in two representative sections pictured in Figure 2. The mean maximum ( $\pm$ SE) weight gain of these seven rats with lesions within 20 days after surgery was  $21.7 \pm 0.6$  g, while the eight rats with sham lesions demonstrated a mean weight loss of  $-6.1 \pm 2.7$  g (see Fig. 3), yielding a difference of 27.8 g ( $t = 8.00$ ,  $df = 13$ ,  $p < .001$ ,  $g = 4.14$ ). The rats with unsuccessful lesions demonstrated a mean weight gain of 2.3 g. The mean daily food intake of the rats with lesions during the period of maximum weight gain (postoperative Days 4-10) was  $27.8 \pm 1.5$  g compared to  $17.9 \pm 0.5$  g for controls ( $t = 6.57$ ,  $df = 13$ ,  $p < .001$ ,  $g = 3.40$ ).

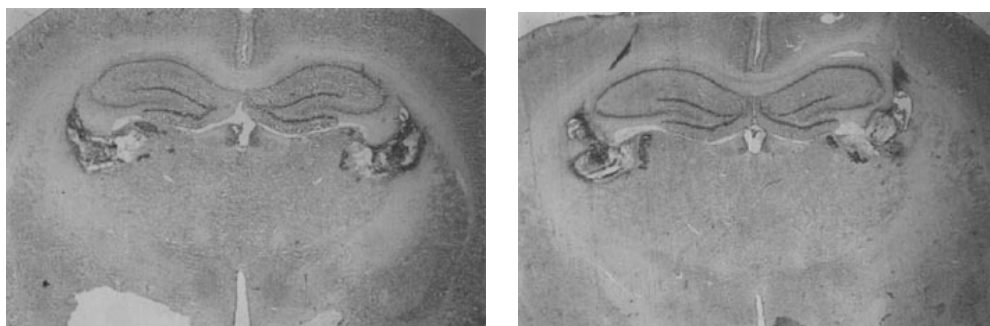


Figure 2. Representative lesions of the dorsal stria terminalis in coronal brain sections taken from two different rats. Significant bilateral damage can be seen at the point where the stria terminalis reaches its dorsal-most extent, before it splits into dorsal and ventral components.

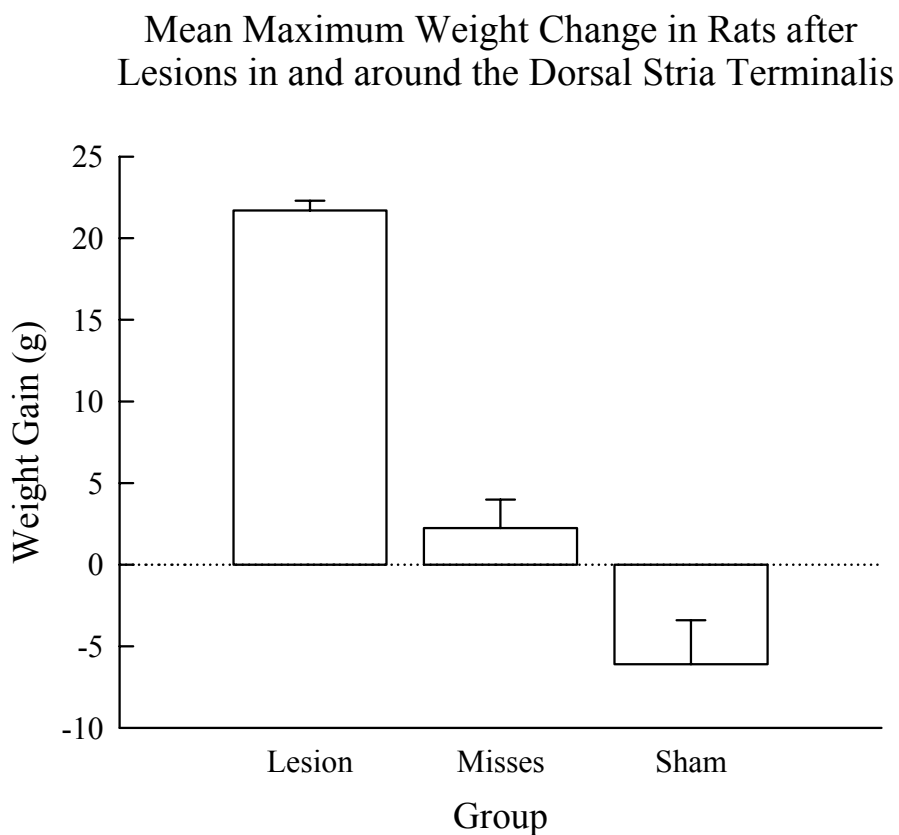


Figure 3. Mean maximum weight change in rats after lesions of the dorsal stria terminalis. Rats with lesions of the dorsal stria terminalis ( $n = 7$ ) gained significantly more weight than did rats with sham lesions ( $n = 8$ ). Rats in the Misses group ( $n = 4$ ) sustained lesions that missed the intended target. Error bars represent standard error.

### Anterior Ventromedial Hypothalamus

This study had to be terminated 15 days postoperatively due to a power outage in the animal colony that caused a dramatic increase in room temperature and a corresponding weight loss in all of the rats. Upon histological examination, six rats were found to have properly placed bilateral knife cuts that were posterior to the optic chiasm but in front of the most anterior portion of the VMH (see Fig. 4). The mean weight gain of these six rats was  $40.3 \pm 6.2$  g in 15 days, while that of the seven rats with sham knife-cuts was  $0.3 \pm 4.8$  g ( $t = 5.17$ ,  $df = 11$ ,  $p < .001$ ,  $g = 2.88$ ) (see Fig. 5). These results are conservative as one control animal was eliminated due to an excessive weight loss of  $-41$  g (no reason apparent except for surgery), and two rats with knife-cuts were eliminated because it appeared that the cuts possibly entered the most anterior shell of the VMH. These last two animals demonstrated weight gains of  $+54$  g and  $+98$  g. The other animals receiving knife cuts were disregarded due to cuts that were anterior to or through the optic chiasm ( $n = 4$ , mean maximum weight change of  $0$  g), cuts that did not extend to the base of the brain ( $n = 1$ , maximum weight gain of  $13$  g), or cuts that could not be visualized ( $n = 1$ , maximum weight gain of  $15$  g). One animal died shortly after surgery and two were euthanized due to eye infections that were probably the result of misplaced cuts that damaged the optic tract. The mean daily food intake of the rats with knife cuts during the period of maximum weight gain (postoperative Days 3-6) was  $25.4 \pm 1.7$  g compared to  $16.8 \pm 1.4$  g for controls ( $t = 3.91$ ,  $df = 11$ ,  $p < .01$ ,  $g = 2.94$ ).

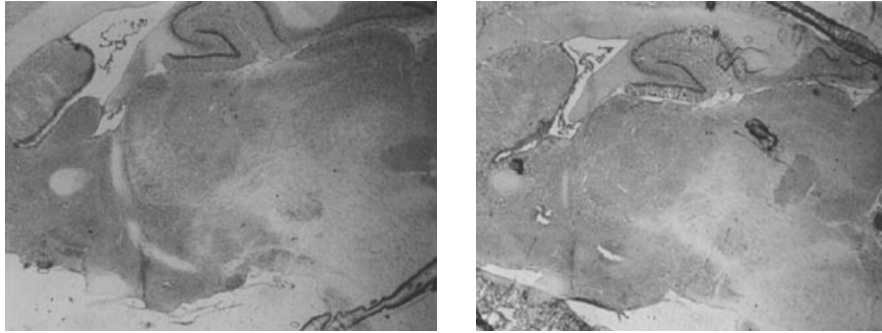


Figure 4. Representative coronal knife-cuts anterior to the VMH in sagittal brain sections taken from two different rats. Damage may be seen just caudal to the optic chiasm toward the base of the brain in the area anterior to the VMH.

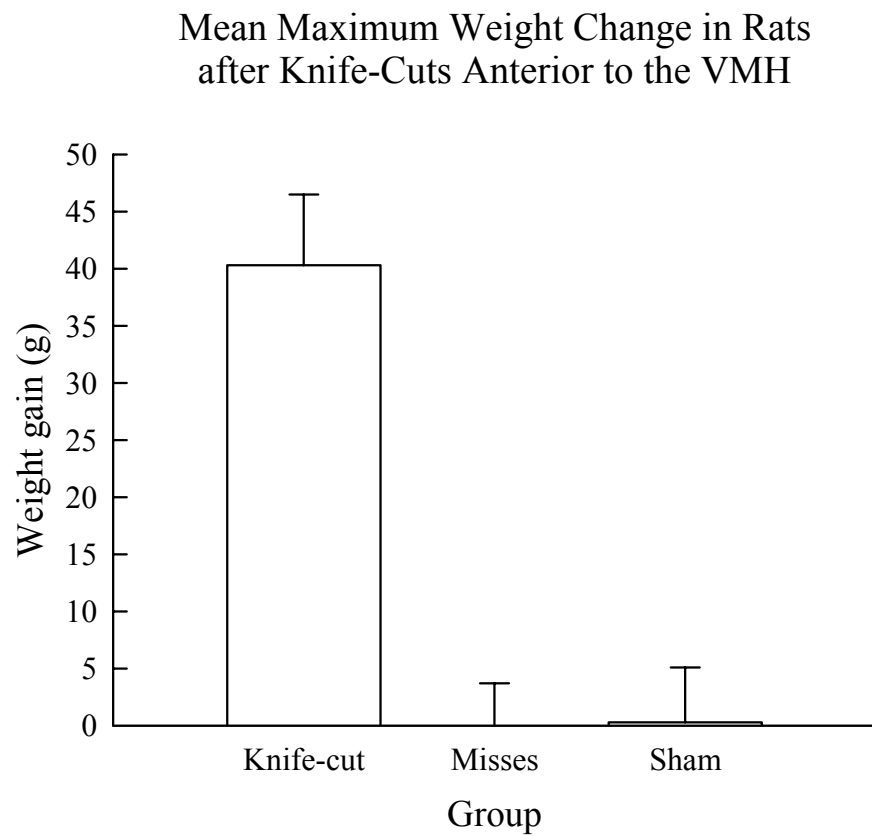


Figure 5. Mean maximum weight gain in rats after coronal knife-cuts anterior to the VMH. Rats with knife-cuts ( $n = 6$ ) gained significantly more weight than rats with sham cuts ( $n = 7$ ). Rats in the Misses group ( $n = 4$ ) sustained incorrectly placed knife-cuts through or anterior to the optic chiasm. Error bars represent standard error.

The brains of three rats were sent away for professional mult-brain amino-cupric silver staining. In the control rat that received a sham cut (i.e., the cannula was lowered into the brain but the knife blade was not extended), there was no manifestation of anterograde degeneration. In the two rats that did receive cuts, in one rat (A) the midsection of the VMH was severed in one hemisphere while the other hemisphere sustained a cut anterior to the VMH, and the other rat (B) had bilateral cuts anterior to the VMH. Rat A evidenced a diffuse pattern of degeneration in the ipsilateral VMH posterior to the midsection cut of the VMH. Moderate to heavy degeneration was seen in the shell of the VMH in rat B (see Fig. 6), and in the hemisphere of rat A that received a cut anterior to the VMH. Both animals evidenced moderate to heavy degeneration in the premammillary nuclei, the lateral septal area, and the habenula, and light degeneration in the nucleus accumbens. Moderate degeneration was also seen in the ventral hippocampus of Rat A. No evidence of damage or degeneration was seen in the PVN of either rat.

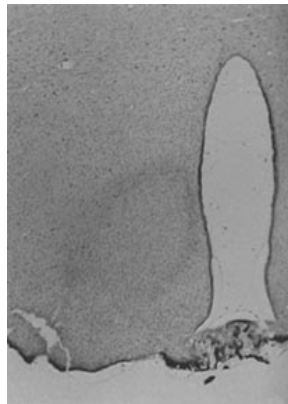


Figure 6. Cupric-silver stain of degenerating terminals in the shell of the VMH after coronal knife-cuts anterior to the VMH.

### Ibotenic Acid

Careful histological examination revealed no evidence of the cell loss or gliosis that one would expect after ibotenic acid lesions, except in one animal. This animal gained 34 g by

postoperative day 20. The weight change of the rats in the control group over the same time period ranged from -16 g to 20 g.

## Discussion

### Dorsal Stria Terminalis

Significant weight gains were observed in female rats with lesions of the dorsal stria terminalis as compared to rats with sham lesions. This differs from previous studies which found no changes in food intake or weight gain using male rats (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975), but coincides with the findings of King, Rollins, et al. (2003) that showed weight gains in female rats after transection of the stria close to its origin. Again, the lack of results in previous studies is attributed to the use of male rats as lesions of the PDA and the VMH produce greater weight gains in female rats (Cox et al., 1969; King et al., 1999; King & Frohman, 1982; Singh, 1970; Valenstein et al., 1969).

While it might appear that these structures produce sex-specific weight gains in females, it should be noted that males do gain weight, but the weight gain often becomes insignificant when it is compared to that of normal male controls. In a study that examined the sex difference found after PDA lesions, male rats gained as much as female rats (approximately 58 g) over the course of 21 days (King et al., 1999). However, females with sham lesions gained approximately 11 g while the male shams gained 34 g during the same time (King et al., 1999). Thus, the sex differences observed after PDA lesions could be magnified by the normal weight gain of male rats, and it may be of interest to examine the effects of these lesions in less sexually dimorphic animals. Unfortunately, studies using other species have not made formal comparisons between males and females, though hyperphagia and/or weight gain have been noted in male dogs with amygdala lesions (Fonberg, 1971) and in human males after removal of the amygdala and other temporal areas (Marlowe, Mancall, & Thomas, 1975; Terzian & Ore, 1955). Other studies employing mixed groups of both male and female cats have reported weight gains and/or

hyperphagia, though the sex of the particular cats displaying these effects was not noted (Green, Clemente, & deGroot, 1957; Morgane & Kosman, 1957; Wood, 1958).

Estrogen does not appear to play a role in the observed sex differences as PDA lesions do not significantly disrupt the estrous cycle, and ovariectomy produces additional weight gain in rats with PDA lesions, indicating different mechanisms (King et al., 1999). Ovariectomy after VMH lesions also results in additional weight gain, though it does not appear to be completely additive (King & Cox, 1973; King et al., 1999; Valenstein, Cox, & Kakolewski, 1969). Moreover, VMH lesions do appear to disrupt the estrous cycle at least temporarily (Hetherington & Ranson, 1942; Sclafani, 1971). It should also be noted that gonadectomy of males eliminates the sex difference seen after VMH lesions (Kemnitz, Goy, & Keesey, 1977). Gonadal atrophy occurs after VMH lesions (Brooks & Lambert, 1946), and by itself, results in increased growth and weight gain in females while causing decreased growth and weight loss in males (Kakolewski, Cox, & Valenstein, 1968).

The weight gain observed in this study ( $21.7 \pm 0.6$  g for the rats with lesions as compared to  $-6.1 \pm 2.7$  g for rats with sham lesions, yielding a net gain of 27.8 g within 20 days) was less than the gains (35.8 g net gain in 20 days) observed in the study which severed the stria close to its origins (King, Rollins, et al., 2003) and less than that typically observed with PDA lesions (50-80 g in 20 days). However, the lesions of the dorsal stria terminalis in the current study were sizable and often included damage to surrounding structures, such as the internal capsule, thalamic nuclei, and the striatum. Thus the weight gain may have been attenuated by damage to surrounding motor areas, just as damage to the overlying globus pallidus attenuates weight gain observed in PDA lesions (King, Cook, et al., 2003; King, Rollins, et al., 2003; Rollins & King, 2000). Moreover, PDA lesions result in less weight gain than VMH lesions (Brooks & Lambert,



1946; King & Gaston, 1977), so it is probable that the PDA/stria terminalis pathway is not the only influence on the VMH involving the regulation of food intake and body weight.

#### Anterior Ventromedial Hypothalamus

Severing the stria farther along its course, just before it enters the VMH, also resulted in weight gain ( $40.3 \pm 6.2$  g within 15 days) in female rats. This gain is commensurate with that observed in rats with PDA lesions (50-80 g in 20 days) and that observed in rats with knife cuts of the stria terminalis close to its origins ( $35.9 \pm 2.5$  g in 20 days) (King, Rollins, et al., 2003). Although the present study had to be terminated after 15 days due a power outage that resulted in an increase in the temperature of the rat colony and a concomitant drop in body weight of the experimental animals, the rate of weight gain of the rats had already slowed considerably, and thus additional weight gains would be unexpected as it is probable they were entering a static phase wherein the higher body weight is maintained but no more gain occurs. This is similar to VMH and PDA rats, which are known to go through dynamic and static phases (Brooks & Lambert, 1946; King, Cook, et al., 1996). The rats with dorsal stria lesions also evidenced this trend.

Some earlier studies also found weight gains in female rats with coronal knife cuts anterior to the VMH (Grossman, 1971; Palka et al., 1969; Storlien & Albert, 1972). Due to differences in methodology and data collection/presentation, it is somewhat difficult to compare the current results with results obtained from previous studies. For instance, in the study of Palka et al., body weight data is presented as the average weight of the rats 6 months after operation. Rats with knife cuts anterior to the VMH weighed 431 g on average compared to 397 g for controls at this time, yielding an average gain of 34 g for the rats with knife cuts. Female rats in the Grossman (1971) study gained an average of 35 g before their weight reached a plateau at

approximately 21 days postoperatively. It is probable that the rats in the first study (Palka et al., 1969) also plateaued at some point, maintaining their higher body weight. Thus, these weight gains are very similar to the ones observed in the present study.

Female rats in the Storlien and Albert (1972) study also gained an average of 35 g, though in a much shorter time period (5 days). However, the rats in the Grossman study had already gained 25 g 5 days postoperatively and were being fed powdered food, which even unoperated rats seem to consider unpalatable (King, Rossiter, et al., 1997), while the rats in the Storlien and Albert study were fed pellets and wet mash. The average weight gain in the present study at postoperative day 5 was 24 g. While this might be less than expected in comparison to the Storlien and Albert study, it is very similar to the 5-day gains in the Grossman study, though the rats in that study were being fed powdered food and the rats in the present study were fed pellets. It should be noted that the selection criteria for the present study were strict, and those rats that gained the most were excluded based on possible infringement of the VMH. Moreover, it has already been concluded by the lesser weight gains in animals with PDA and stria lesions as compared to VMH lesions that the stria is probably only one of several influences on the VMH as regards feeding and body weight regulation (see above).

Two previous studies failed to note any effects after knife-cuts anterior to the VMH. One of these studies used male rats (Voloschin et al., 1968), and as previously noted, weight gains in related areas are much more prominent in female rats. The other study finding no weight gain after anterior hypothalamic knife cuts used female rats but provided unpalatable powdered food (Sclafani, 1971). None of the above studies verified that the cuts severed fibers terminating in the VMH.

### Anterograde degeneration.

In the present study, anterograde degeneration analysis was performed and degenerating terminals were found primarily in the shell of the VMH, the premammillary nuclei, the lateral septal area, and the habenula after coronal knife-cuts anterior to the VMH. This pattern is very similar to the anterograde degeneration observed after PDA lesions, wherein the shell of the VMH, lateral septal area, nucleus accumbens, and habenula are also prominently stained (King, Cook, et al., 2003). Interestingly, lesions of the septal area in female rats have been reported to result in mild hyperphagia by some researchers (Singh & Meyer, 1968; Wetmore & Nance, 1991).

The dorsal component of the stria terminalis is known to include fibers that terminate in the premammillary nuclei, as well as the shell of the VMH, where it is thought that they synapse with dendrites protruding from the VMH (de Olmos, 1972; Heimer & Nauta, 1969). The pattern of anterograde degeneration in the shell of the VMH observed in the current study is almost identical to the anterograde degeneration seen after amygdala lesions (de Olmos, 1972), and more specifically, lesions of the PDA (King, Cook, et al., 2003). The bed nucleus of the stria terminalis, part of which is included in PDA lesions, has also been found to project mainly to the shell of the VMH rather than the core (Luiten & Room, 1980; Swanson & Cowan, 1979; Zaborsky, 1982). Though the shell of the VMH is regarded as a cell-poor area in comparison to the core, it is well-populated with cell bodies and dendrites from the VMH (Heimer & Nauta, 1969). Thus the VMH is regarded as the primary target of stria fibers terminating in this region (Heimer & Nauta, 1969). Indeed, electrical impulses coursing through the stria inhibit the VMH and electrical stimulation of the corticomедial amygdala produces no response in the VMH if the stria terminalis is cut (Dreifuss, Murphy, & Gloor, 1968).

## Ibotenic Acid

The prior two procedures confirm that the stria terminalis is carrying feeding related information to the hypothalamus. Unfortunately, the present study can not confirm that this feeding related information originates in the amygdala, though the weight gain of the one animal that did seem to sustain cell loss in the PDA is provocative. The failure to detect damage to the amygdala after ibotenic acid lesions could be due to several factors. For instance, it is possible that acid injected did not reach the target, diffusing up the electrode track instead. Precautions were taken to minimize this possibility: the acid was injected over the course of 1 minute and the cannula was left in place for 5 minutes afterwards, a procedure recommended for such infusions (Jarrard, 1993). Alternatively, the cannula tip may have been clogged, though this possibility was also minimized by filling the cannula with 0.3 ul for each lesion, evacuating 0.1 ul before and after each intra-cerebral injection. It is also possible that the ibotenic acid was sucked into the nearby ventricles, as the PDA is bordered dorsally and posteriorly by the inferior horns of the lateral ventricles (see Fig 7).

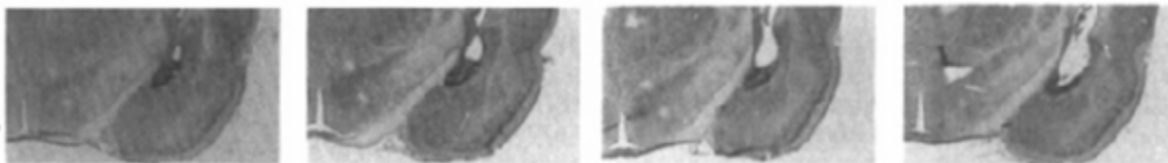


Figure 7. Series of brain sections from one rat showing a PDA lesion in relation to the inferior horn of the lateral ventricle. From left to right, each picture portrays more posterior levels and the ventricle becomes more apparent. From Rollins & King, 2000 (Fig. 1B, p. R1350).

The concentration and volume of the ibotenic acid injected was that recommended for such studies (Jarrard, 1993). Using a higher concentration of ibotenic acid is problematic as it is difficult to get the powdered acid into solution (Jarrard, 1993). Moreover, the use of higher volumes of ibotenic acid increases the possibility of spread to neighboring sites (Jarrard, 1993).

While some evidence suggests that high doses of ketamine may offer protection against the neurotoxic effects of ibotenic acid (Lees, 1989), normal doses of ketamine were used in the present study. Additionally, preliminary results of another ongoing study in the laboratory using the same batch of ibotenic acid and the same methodology to lesion the septal area suggest that the procedure is efficacious (i.e., the lesion has resulted in septal irritability). This again may point to an issue involving acid seepage into the closely adjacent lateral ventricles or to specific architectural properties of the amygdala itself, specifically the PDA as ibotenic acid was successfully injected ventrally in the basolateral amygdala as part of a pilot study (see Fig. 8). Also, in another pilot study, using different volumes of ibotenic acid to lesion the PDA proved unsuccessful, though injecting methylene blue instead of ibotenic acid did produce a stain in the intended area but with apparent diffusion. In addition, the present study has been attempted subsequently with similar results (i.e., lesions could not be found upon histological examination).

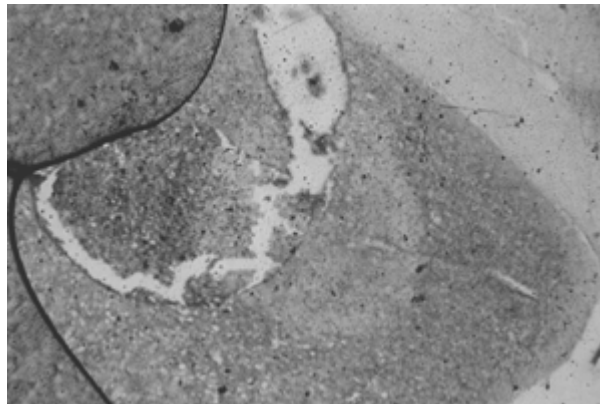


Figure 8. Successful ibotenic acid lesion of the basolateral amygdala. The lesion can be seen as a light tear-drop-shaped area in the center of the photograph.

While ibotenic acid may prove to be an important means by which to determine whether cell bodies within the amygdala or fibers of passage are responsible for the effects of PDA lesions, it is not without its faults. Damage to axons does occur at some sites and cell loss may be

incomplete (Kohler & Schwarcz, 1983; Salinas, Parent, & McGaugh, 1996). Evidence suggests that the amygdala is among some of the brain structures resistant to quinolinic acid, a neurotoxin with similar effects to ibotenic acid (Schwarcz & Kohler, 1983). Also, Kohler and Schwarcz discovered a few brain structures that proved resistant to the neurotoxicity of ibotenic acid, though the amygdala was not among the structures tested.

Other researchers have used ibotenic acid to successfully lesion the amygdala (i.e., Lorenzini et al., 1991; Morris, Frey, Kasambira, & Petrides, 1999; Salinas et al., 1996; Touzani, Taghzouti, & Velley, 1997), though they often used higher than recommended amounts or concentrations. Interestingly, Touzani et al. (1997) could not find evidence of damage to their intended target, the central nucleus of the amygdala, in 11 of 25 lesioned rats. As noted above, it is difficult to produce more concentrated solutions of ibotenic acid and diffusion is made more probable by using greater volumes (Jarrard, 1993). Moreover, the diffusion of ibotenic acid appears to be particularly problematic in the amygdala (Sakai & Yamamoto, 1999; Yamamoto, Fujimoto, Shimura, & Sakai, 1995).

### The Stria Terminalis

The results of the present study add additional support to the idea that the dorsal component of the stria terminalis exerts an inhibitory influence on the VMH in the regulation of food intake and body weight. Many researchers dismissed the stria terminalis in this respect because of inconsistent findings after destruction of the stria terminalis itself (Black & Weingarten, 1988; Box & Mogenson, 1975; Myhrer, 1975; Sclafani, 1971; Voloschin et al., 1968) and its main input, the amygdala (see Rollins & King, 2000 for a review). Even the role of the stria's most relevant target in this respect, the VMH, has recently been called into question (see below). However, support for all these structures in the regulation of food intake and body

weight accumulates. Aside from the current findings and those discussed previously, transections of the stria or destruction of the VMH have been found to prevent the normal suppression of ingestion that results from stimulation of the medial amygdala (White & Fisher, 1969).

While the stria is the most direct route by which the medial amygdala may influence the hypothalamus, other pathways exist. The medial amygdala may also reach the VMH indirectly via the hippocampus and lateral septum, and also via several divisions of the bed nucleus of the stria terminalis (Dong, Petrovich, & Swanson, 2001; Dong & Swanson, 2004; Petrovich, Canteras & Swanson, 2001). However, it should be noted that these pathways are believed to be involved more with reproductive and defensive functions (Dong et al., 2001; Dong & Swanson, 2004; Petrovich et al., 2001).

Other pathways by which the amygdala may influence feeding behavior is through direct input from the central nucleus to the lateral hypothalamus (Petrovich et al., 2001) or via indirect inputs to the PVN via the rhomboid nucleus of the bed nucleus of the stria terminalis (Dong & Swanson, 2003). However, given the pattern of fiber degeneration following PDA lesions (King, Cook, et al., 2003) and the knife-cuts in the present study, it seems unlikely that the PVN or the lateral hypothalamus play a major role in the weight gains and hyperphagia observed after PDA lesions or the results reported herein.

### The Hypothalamus

Additional support for the proposition that the lateral hypothalamus and the PVN are not involved comes from studies in which no changes in activity were found in the lateral hypothalamus after amygdala stimulation (Gloor, 1955) or stimulation of the supra-commissural division of the stria terminalis (Sutin, Orden, & Tsubowkawa, 1963). Moreover, ibotenic acid lesions of the bed nucleus of the stria terminalis (an area closely related to the amygdala and stria

terminalis with common afferent and efferent pathways) result in a decrease in the amount of cell bodies expressing enkephalins in the VMH, while no changes were found in the PVN (Vankova, Boyer, Leviel, & Arluison, 1996).

Clearly, the VMH should not be prematurely dismissed as has been the recent trend brought about by one study that found no effects on body weight or food intake after lesions restricted to the ventromedial nucleus of the hypothalamus (Gold, 1973), as well as the discovery of increased body weight and hyperphagia after lesions of the PVN (Aravich & Sclafani, 1983; Leibowitz et al., 1981). Decades of research support a role for the VMH in this regard, as does significant differences observed in the constellation of effects after VMH and PVN lesions (King et al., 1989; Tokunaga et al., 1986; Weingarten, Chang, & McDonald, 1985). Moreover, degeneration is seen in the VMH but not the PVN after PDA lesions (King, Cook, et al., 2003) and unilateral PDA lesions placed ipsilateral to unilateral VMH lesions do not result in the weight gain observed when these lesions are placed contralateral to each other (Grundmann et al., 2005), an indication of common mechanisms.

### The Amygdala

Previously, many researchers dismissed the role of the amygdala in food intake and body weight due to inconsistent findings (see Rollins & King, 2000 for a review). However, many lines of evidence indicate that the amygdala is involved with these functions. On a cellular level, neurons in the centromedial amygdala have been found to be responsive to glucose (Lenard et al., 1989). Moreover, neurons that respond to taste stimuli have been found in the amygdala of rats (Yamamoto, Azuma, & Kawamura, 1981), rabbits (Schwartzbaum & Morse, 1978) and primates (Nishijo, Ono, & Nishijo, 1988a, 1988b; Sanghera, Rolls, & Roper-Hall, 1979). In primates, not only do cellular recordings indicate that neurons in the amygdala respond to taste,



they also respond to the smell, and sight of food, as well as to other stimuli associated with food through learning (Nishijo et al., 1988a; Rolls, Yaxley, & Sienkiewicz, 1990; Sanghera et al., 1979). Likewise, in humans, regional cerebral blood flow in the amygdala and only the amygdala was found to positively correlate with subject ratings of the incentive value of potential foods (Arana et al., 2003).

Neurons in the amygdala appear also to be sensitive to satiation while activation/deactivation of the amygdala has varying effects. The activity of the cells in the primate amygdala that respond to food and associated stimuli is inhibited with satiation (Critchley & Rolls, 1996; Rolls, Sienkiewicz, & Yaxley, 1989; Scott, Yan, & Rolls, 1995; Yan & Scott, 1996). Similarly, Gautier et al. (2001) found deactivation in the amygdala of obese women as a result of satiety. Also, electrical stimulation of the amygdala results in cessation or reduction of food ingestion in monkeys (Robinson & Mishkin, 1962) cats (Fonberg & Delgado, 1961) and rats (Grossman, 1964).

Support for the role of the amygdala in ingestion and body weight regulation also comes from research investigating the results of lesions. Studies involving humans with damage to the amygdala report hyperphagia and/or altered feeding behavior (Marlowe et al., 1975; Rozin, Dow, Moscovitch, & Rajaram, 1998; Terzian & Ore, 1955). Additionally, examination of published photographs in studies reporting weight gains after amygdala lesions in cats (Green et al., 1957, Figs. 17 and 18, p. 543) and dogs (Fonberg, 1976, Fig. 5b, p. 73) reveals that successful lesions included damage to a common area near the dorsal tip of the optic tract, comparable to the PDA in rats (Rollins & King, 2000). Lesions that did not produce weight gain (Green et al., 1957, Figs. 19 and 20, p. 543) were more ventral and did not include this area (Rollins & King, 2000). Wood (1958) did not publish photographs though the damage described probably included the

proposed critical area (Rollins & King, 2000). Lesions in the Morgane and Kosman study (1957, Fig. 1, p. 159) also probably involved the critical area as their lesions were large and destroyed almost the entire amygdala. Obesity was observed in only one cat in the study by Koikegami et al. (1958, Fig. 1, p. 215), and the lesion in this animal did indeed infringe upon the critical area at the dorsal end of the optic tract.

Likewise, significant increases in body weight and food intake as a result of lesions to the PDA have been replicated in many studies (King, Arceneaux, et al., 1996; King, Cook, & Dallman, 1996; King, Cook, et al., 1996; King, Kass, Cadieux, et al., 1993; King, Kass, Neville, et al., 1993; King et al., 1999; Rollins & King, 2000). Unfortunately, without the confirmation that successful neurotoxic lesions would provide, the role of the PDA in food intake and body weight remains unclear. However, it should be noted that lesions of surrounding areas that contribute fibers of passage running through the PDA do not result in weight gains (Rollins & King, 2000). Also, PDA lesions elevate plasma insulin levels (King, Cook, & Dallman, 1996), alter leptin intake (Banks et al., 2001), and curtail feeding stimulated by 8-OH-DPAT (Coscina et al., 2000).

Overall, the amygdala seems to be activated during anticipatory states wherein food and stimuli associated with food are present (Burns, Robbins, & Everitt, 1993; Everitt, 1990), and deactivated as satiety progresses (Critchley & Rolls, 1996; Rolls et al., 1989; Scott et al., 1995; Yan & Scott, 1996). Thus the amygdala may function to inhibit feeding until conditions are favorable for ingestion to proceed. This would explain the effects of lesion studies in rats and humans as well as the cessation of eating observed upon amygdala stimulation. The amygdala also may mediate the devaluation of food as satiety progresses via dopaminergic influences (see below), with lesions preventing this devaluation resulting in the continuation of feeding.

The amygdala has long been suspected as a site wherein sensory stimuli are evaluated in accordance with their current relevance based on prior associations and the biological needs of the organism. Accordingly, the amygdala receives information from sensory areas, including significant efferents from olfactory (e.g., Lammers, 1972) and taste areas (Levy et al., 1999; Norgren, 1976; Scott et al., 1993; Yan & Scott, 1996; Yasui, Itoh, & Mizuno, 1984) as well as visceral information concerning the gut (Aggleton, Burton, & Passingham, 1980; Woods, Seeley, Porte, & Schwartz, 1998). The amygdala does not seem to function in the discrimination of stimuli per se but rather determines the biological, motivational, and emotional significance of sensory input (LeDoux, 2000; Morris & Dolan, 2001; Rolls, 2000; Scott et al., 1993; Small et al., 1997; Touzani et al., 1997; Yan & Scott, 1996).

Given the connections of the amygdala, it is in a prime position to act as a liaison between the hypothalamus and sensory areas, modulating incoming olfactory and taste information according to past experience, current biological needs, and the external resources available to fulfill these needs, and sending this information along the stria terminalis to the hypothalamus, where it is used to indicate whether feeding should proceed or not (Arana et al., 2003; Morris & Dolan, 2001; Murray & Wise, 2004; Rolls & Rolls, 1973; Small et al., 1997; Touzani et al., 1997; Turner, Mishkin, & Knapp, 1980).

The amygdala has the ability to influence dopamine (DA) efflux in the nucleus accumbens via a GABA-ergic projection to dopaminergic neurons in the ventral tegmental area (VTA) (Fudge & Haber, 2000; Wallace, Magnuson, & Gray, 1992; Phillips, Ahn, & Howland, 2003). These ventral tegmental neurons in turn regulate the efflux of dopamine in the nucleus accumbens (Phillips et al., 2003). Accordingly, inactivation of the central nucleus in rats using lidocaine resulted in a significant decrease in DA efflux in the nucleus accumbens while

stimulation produced no results (Phillips et al., 2003). The influence of the amygdala on dopamine efflux in the nucleus accumbens is relevant, as this provides a means by which the amygdala may influence the motivational relevance of stimuli depending on biological status (Phillips et al., 2003). Both DA efflux (Phillips et al., 2003) and activity in the central nucleus (Uwano, Nishijo, Ono, & Tamura, 1995) are increased during feeding. Inactivation of the central amygdala nucleus led rats to feed even after the effects of satiety were expected to diminish food intake and abolished the normal anticipatory DA release when food was detected but access prevented (Phillips et al., 2003). It is possible that without the central nucleus, rats were unable to detect the declining reward value of the food as satiety progressed (Phillips et al., 2003).

The amygdala also receives inputs from the VTA (Saper, 2000). Thus activation of the central amygdala during the initial stages of feeding may disinhibit DA release in the nucleus accumbens via the VTA. As satiation occurs, a feedback loop involving the VTA may inhibit the amygdala, decreasing DA efflux in the nucleus accumbens and signaling a decline in the reward value of food. Accordingly, satiation results in a deactivation of both the amygdala and the nucleus accumbens in obese women (Gautier et al., 2001). Perhaps PDA lesions disrupt this proposed feedback loop. Unable to assess the declining reward value that comes with satiety (Ahn & Phillips, 2003), the amygdala may continue to send messages to the hypothalamus indicating that eating should occur. Concordant with this is the purported greater involvement of the amygdala in negative emotions (see Zald & Pardo, 1997). The amygdala may register the decrease in the positive aspects of food that occurs with satiety (Ahn & Phillips, 2003) via visceral inputs from brainstem nuclei (Aggleton et al., 1980; Woods, Seeley, Porte, & Schwartz, 1998). Without the amygdala then, the reinforcement value of food may not decline with satiety.

### Current and Future Directions

In sum, research from the current study supports a role for the stria terminalis in feeding and body weight regulation via the hypothalamus. However, once again, the precise role of the amygdala, specifically the PDA, proves elusive. Nevertheless, it is clear that the amygdala and the VMH can not continue to be dismissed as regards feeding and body weight regulation. Future research should investigate the roles of the various neurotransmitters and peptides that act within the amygdala-stria terminalis-VMH circuit. Meanwhile, the septum, another notable target of the stria terminalis, is currently being evaluated for its role in feeding and body weight regulation. Also, given the substantial olfactory input to the amygdala (see Lammers, 1972), research is being planned to investigate the effects of olfactory bulbectomy on feeding and weight regulation and how it may affect the weight gain observed after PDA lesions. Notably, olfactory bulbectomy performed in VMH-lesioned female rats that are obese and in a static phase results in a new phase of additional weight gain (Larue & Le Magnen, 1970).

Given the importance of olfaction in sexual behavior, as well as the probable role of the amygdala in the sexual disturbances observed in the Kluver-Bucy syndrome (i.e., Kluver & Bucy, 1939; Kupfermann, 1991; Schreiner & Kling, 1953; Terzian & Ore, 1955; Wood, 1958), and the fact that the VMH has terminals that mediate sexual behavior (see Canteras et al., 1994), the amygdala-stria terminalis-VMH circuit should be studied for its possible role in the mediation of sexual activity. Interestingly, the pattern of degeneration observed after PDA lesions bears a striking resemblance to the circuit proposed by Winans Newman (1999) for sexual behavior.

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## Appendix

# University of New Orleans

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## Institutional Animal Care and Use Committee (IACUC)

**DATE:** November 13, 2002  
**TO:** Bruce M. King, Ph.D.  
**FROM:** Gerald J. LaHoste, Ph.D.  
Chairman  
**RE:** *IACUC Protocol No. 049*  
*Entitled: A rat model of the Kluver-Bucy syndrome*

Your application for the use of animals in research (referenced above) was reviewed by the full IACUC on November 12, 2002. The application was approved with the provision that you address to the Chair's satisfaction the following points (referenced by item number on the application form) in a separate letter or memo:

10. Please give name of USDA-approved vendor for the cat. "Hamster" is misspelled.
12. Please give weight of hamsters and guinea pigs. "Young adults" is not sufficient.
14. Please check or circle "E," and delete text entered.
15. Please check "No." Because the cat will be allowed to move this is not considered restraint.
18. Please supply chemical name of "Setazine." Please give dosages in mg/kg.
19. Please respond "none" or "N/A."
22. Please state that CO<sub>2</sub> is compressed. Please state that decapitation will be without anesthesia and state why.
27. Under "stereotaxic surgery" line 2, ketamine alone is insufficient anesthesia. Please state adjunct drug (e.g., the chemical name of Setazine). Under "fear responses" the second word should be "rats" not "cats."

## Vita

Bethany Rollins was born in Ohio and grew up in West Virginia. She attended Ohio University, initially majoring in pre-med chemistry in the honors college before pursuing her interest in psychology. She completed an honors thesis in her senior year on the behavior of domestic cats in response to varying doses of catnip. As a senior, she graduated magna cum laude, receiving honors from Phi Kappa Phi and the Psychology department. Since then, she has been studying the effects of amygdala lesions on body weight, feeding, and other behaviors with Dr. Bruce King at the University of New Orleans. She obtained her M.S. in 1999 and was elected graduate student of the year in 2001.